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(54) Title: METHOD FOR PRODUCING BETA FORM OF CRYSTALLINE ANHYDROUS AZTREONAM

(57) Abstract: A process is described for producing anhydrous β-form of ((Z)-2-[[[(2-amino-4-thiazolyl)[[*trans*-(2S,3S)-2-methyl-4-oxo-1-sulfo-3-azetidinyl]carbamoyl]methylene]amino]oxy]-2-methylpropionic acid (also known as Aztreonam).

DETAILED DESCRIPTION OF THE INVENTION

The instant invention relates to a novel process to produce highly pure sterile crystalline anhydrous Aztreonam β-form. The present invention enables the preparation of a solution of the α-form Aztreonam in absolute ethanol without using trialkylamine or silylating agent, and this solution can be sterile filtered to crystallise sterile β-form.

Specifically, the instant invention involves dissolving the α-form in absolute ethanol at low temperature. The α-form of Aztreonam dissolves in absolute ethanol at a temperature varying from -10°C to +15°C and crystallizes out as β-form on raising the temperature to 50°C to 55°C. Crystallization of Aztreonam does not occur from this solution if maintain at -10°C to +15°C. This unusual solubility characteristic of Aztreonam α-form has not been reported hitherto in literature. However, similar solubility behaviour of a different antibiotic namely, cefotaxime sodium has been described in US Patent 4,912,211, example 6. Such a solution of α-form can be treated with carbon to remove colour and also can be passed through the 0.2 micron sterile filter for aseptic preparation.

The α-form is dissolved in anhydrous alkanol, preferably absolute ethanol, at -10°C to +15°C, most preferably at 5°C to 10°C. This solution, maintained at this temperature, is treated with activated carbon and is filtered through clarification filter and a sterile filter to obtain a sterile solution. The anhydrous β-form of Aztreonam is then crystallised by raising the temperature of the sterile filtrate to 50°C to 55°C. The product is then filtered and dried in vacuum. The β-form prepared by this process is a suitable pharmaceutical agent for blending with a basic material, such as L-arginine, for intravenous and intramuscular administration.

Major advantage realised in the present invention compared to the prior art is the process simplicity. Prior art procedure requires an additional step wherein addition of trialkylamine or silylation is necessary to dissolve α-form for sterile filtration; in the present procedure, the α-form is directly dissolved in ethanol at low temperature to obtain a solution which is suitable for sterile β-form preparation.

Preparation of the β-form from the α-form can be accomplished by the procedure described in the following preparation.

Example

Aztreonam α-form (40 g) was added to pre-cooled absolute ethanol (2400 ml) at 8-10°C and stirred for 30 minutes to obtain a clear solution. This solution was treated with activated carbon (1 g) for 15 minutes at 8-10°C. The suspension was filtered through celite and the residue was washed with ethanol (50 ml). The filtrate was then warmed to 50-55°C slowly over a period of 2 hours to crystallize β-form. The hot suspension was cooled to 15-20°C, stirred for 1 hour and filtered. The crystals were dried in vacuo to obtain 33 g of the product which was confirmed to be the β-form by IR spectrum, powder X-ray diffraction pattern and differential scanning calorimetry.

INTERNATIONAL SEARCH REPORT

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B. FIELDS SEARCHED

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 070 024 A (SQUIBB & SONS INC) 19 January 1983 (1983-01-19) page 2, line 24 -page 3, line 4; claims; examples 3,6 & US 4 946 838 A 7 August 1990 (1990-08-07) cited in the application	1
A	US 4 826 973 A (ANDERSON NEAL G ET AL) 2 May 1989 (1989-05-02) cited in the application the whole document	1

☐ Further documents are listed in the continuation of box C.

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